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EFFECT OF PASTEURELLA PESTIS TOXIN ON THE  
HISTAMINOPEXIC EFFECT OF THE BLOOD  
OF ALBINO RATS AND GUINEA PIGS

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EFFECT OF PASTEURELLA PESTIS TOXIN ON THE  
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Following is the translation of an article by  
I. V. Domaradskiy and V. I. Krupenina in the Russian-  
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From the biochemical laboratory (Director:  
Professor I. V. Domaradskiy) of the Irkutsk  
Scientific Research Antiplague Institute of  
Siberia and the Far East

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of Medical Sciences USSR N. N. Zhukov-Verezhnikov)

In previous studies it was established that sensitization of animals to histamine induced by plague bacillus and its toxin cannot be explained by inhibition of diaminoxidase activity. This phenomenon is not associated either with the effect toxin has on histamine formation. Therefore, further research in this area studied the effect of plague toxin on the so-called histaminopexic effect, that is, on binding of exogenic histamine by blood serum.

Initially the histaminopexic effect (HPE) was detected in work with normal human blood serum. It was found that HPE occurs in the blood sera of guinea pigs, rats, mice, dogs, and cats; in the blood sera of rabbits, cattle, hogs, horses, and eels it is less pronounced or altogether lacking (9,11). In addition to blood serum, HPE is observed in work with homogenates of different tissues of rats, guinea pigs, and rabbits (4).

There is reason to believe that HPE played no small role in the transfer and detoxification of histamine. Favoring this suggestion, in particular, is the slackening or total absence of HPE in persons suffering with allergic diseases (10, 12),

in guinea pigs sensitized by egg albumen (13) and also in rats deprived of hypophysis, ovaries, or adrenal glands (11,14,15).

#### EXPERIMENTAL METHODS

Instead of 5 percent serum as recommended in (9,11), we used whole citrated blood. The basis for this change was, first of all, our data on the more pronounced HPE in whole citrated blood than in 5 percent serum, and in the second place, data on the similarity of the manifestation of this effect both in serum and in blood (5).

In experiments in vivo one group of white rats weighing 160-180 grams were intraparentally given three LD<sub>50</sub> of plague bacillus toxin (fraction 11 of the EB strain); these animals were decapitated in four hours after injection of the toxin. Another group of white mice were administered in the same way one LD<sub>50</sub> of toxin and sacrificed in 18 hours. Guinea pigs received the same toxin doses, increased on a pro-rated basis with the animal's weight (300-350 grams); they were sacrificed after the same period of time respectively for the two dosage groups, 4 hours and 18 hours<sup>7</sup>.

#### Histaminopexic Effect in the Blood ( $M \pm m$ )<sup>1</sup>

(a) Вид животного	(b) Без токсина (контроль)	C ТОКСИНОМ in vivo		C ТОКСИНОМ in vitro	
		(c) 3 LD <sub>50</sub> через 4 часа после введения	(d) 1 LD <sub>50</sub> через 18 часов после введения	(e) "Small" dose	(f) "Large" dose
Белые крысы . . . . .	56,9 ± 3,1	6,5 ± 1,0	30,7 ± 3,4	63,0 ± 2,5	71,1 ± 1,3
Морские свинки . . . . .	53,9 ± 3,9	4,9 ± 1,6	21,4 ± 1,2	61,7 ± 2,8	69,9 ± 0,9

LEGEND: a) Species of animal; b) Without toxin (control); c) Containing toxin in vivo; d) Containing toxin in vitro; e) 3 LD<sub>50</sub> 4 hours after administration; f) 1 LD<sub>50</sub> 18 hours after administration; g) "Small" dose; h) "Large" dose; i) White rats; j) Guinea pigs.

- 1 In controls -- average data of 10 specimens, in remaining experiments -- 5 specimens.
- 2 In experiments with rat blood "small" doses -- 90 micrograms (3 LD<sub>50</sub>), and with guinea pig blood -- 200 micrograms (3 LD<sub>50</sub>, for rats converted to the guinea pig weight); "large" doses in experiments with the blood of both animal sexes -- one microgram.

The blood of sacrificed animals was collected in test tubes containing citrate (1 microgram per 1 ml of blood). At the same time blood was collected from guinea pigs and white mice which had not been given toxin (control group). Ten micrograms of histaminedichloride in a volume of 1 ml was added to

1 ml of whole citrated blood of experimental and control animals. The mixture was rapidly agitated and placed on ice. In 15 minutes histamine determination was made.

In experiments in vitro only histamine (10 micrograms) was added to a single sample of blood of healthy animals, and to the second -- histamine and plague bacillus toxin in amounts indicated in the table footnotes.

The amount of histamine was determined by the biological method at 38 degrees for the atropinized section of the ileum of the guinea pig suspended in a Ringer-Locke solution, through which oxygen was bubbled. The error was  $\pm$  3.5 per cent. Binding of histamine was calculated by its disappearance in samples containing citrated blood and expressed in percentages of the standard histamine dose, equal to 1 microgram. All the conclusions were drawn after statistical treatment of the results according to the method of small samples (3).

#### EXPERIMENTAL RESULTS

As we can see from the table, whole citrated blood of white rats and guinea pigs exhibits the HPE [See Note], in which no substantial difference in the capacity of the blood of both species of animals to bind histamine was found (the probability that the difference is a random one is somewhat greater than 0.05).

([NOTE] Its intensity depends to some extent on the dose of the histamine added: when 5 micrograms of histamine is added its fixation is 18 per cent above the mean value. However, from methodological considerations we used a larger dose of histamine -- 10 micrograms.)

From this same table it follows that after administration of the plague bacillus toxin HPE in animal blood diminished sharply. This was especially striking after four hours following administration of 3 LD<sub>50</sub> of toxin, but even after 18 hours following administration of 1 LD<sub>50</sub> of toxin the HPE in the blood continued to remain weakly pronounced.

Another picture was observed in experiments in vitro; the addition of "small" toxin doses to the blood samples taken from healthy animals did not inhibit HPE. When the same toxin dose was used, equal to 1 microgram per sample, we even noted a certain intensification of histamine fixation by the blood (the probability of error is less than 0.01).

Accordingly, it is of some interest to note that after we determine histamine in the blood samples containing "large" toxin doses for complete relaxation of the ileum section, we had to twice change the Ringer-Locke solution in which the ileum had been placed. Upon determination of histamine in the blood

samples without the addition of toxin from without (1 microgram), a single replacement of the solution was adequate for this. In and of itself the toxin in this same dosage did not induce contraction of the small intestine, but together with histamine without blood the same reaction was produced as with non-toxin histamine. We did not study in greater detail this characteristic of toxin action in the histamine-containing blood sample.

And thus, one of the ways plague bacillus toxin manifests itself in the animal organism is inhibition of blood HPE. The latter has been observed not only in white rats sensitive to this toxin preparation, but also in guinea pigs, which are relatively resistant to it. This is so because we know that this is a rare case, when the plague bacillus toxin has an effect similar in intensity -- on animals differing in their toxin sensitivity.

The lack of any effect of toxin on blood HPE in experiments in vitro leads to the thought that inhibition of blood HPE in plague intoxication, that is, in experiments in vivo is not a consequence of the direct action of the toxin on the mechanism of histamine fixation, but is caused by some other factors. One of such factors evidently can be found in the damage to the adrenals, which in the opinion of V. V. Donskov (2) are an important factor inducing death in plague infection. As already indicated, from the data of several authors (11, 14) HPE is absent in the serum of rats deprived of their adrenal glands.

Another factor, on which inhibition of HPE depends -- allergic state of the organism (10, 12, 13) -- plays no great role in plague intoxication.

Whether in plague intoxication inhibition of blood HPE is the cause of increased sensitivity of the animal to histamine, it is still difficult to say, since the question of the identity of metabolic pathways of exogenic and endogenic histamine has not been decisively answered (5,7) and the effect toxin has on the liberation of histamine from tissues has remained unstudied [See Note/].

[NOTE/] For the case of several other infections the mechanism of increased animal sensitivity to histamine can be otherwise. For example, when animals are given whooping cough vaccine, it is related chiefly to the activation of histidine-decarboxylase (16), and in brucellosis, evidently is induced by liberation of histamine from a storage point (8).

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